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Research Article | Cardiovascular

Flavopiridol Inhibits TGF- β -Stimulated Biglycan Synthesis by Blocking Linker Region Phosphorylation and Nuclear Translocation of Smad2

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Abstract

Transforming growth factor- β (TGF- β) is a pleiotropic growth factor implicated in the development of atherosclerosis for its role in mediating glycosaminoglycan (GAG) chain hyperelongation on the proteoglycan biglycan, a phenomenon that increases the binding of atherogenic lipoproteins in the vessel wall. Phosphorylation of the transcription factor Smad has emerged as a critical step in the signaling pathways that control the synthesis of biglycan, both the core protein and the GAG chains. We have used flavopiridol, a well-known cyclin-dependent kinase inhibitor, to study the role of linker region phosphorylation in the TGF- β -stimulated synthesis of biglycan. We used radiolabeled incorporation and SDS-PAGE to assess proteoglycan synthesis, real-time polymerase chain reaction to assess gene expression, and chromatin immunoprecipitation to assess the binding of Smads to the promoter region of GAG Synthesizing genes. Flavopiridol blocked TGF- β -stimulated synthesis of mRNA for the

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nucleus and positively regulate transcription. These results demonstrate the validity of the kinases, which phosphorylate the Smad linker region as potential therapeutic target(s) for the development of an agent to prevent atherosclerosis.

Footnotes

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